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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

10/577,982

Applicant(s)

KOIZUMI, MAKOTO

Examiner

MARK STAPLES

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 8-17 and 19-45 is/are pending in the application.
- 4a) Of the above claim(s) 8-11, 44 and 45 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 15-17 is/are allowed.
- 6) ☒ Claim(s) 1-4, 12-14 and 19-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-506)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/20/2010 has been entered.

2. Applicant's amendment of claims 1-4 in the paper filed on 01/20/2010 is acknowledged.

Claims 1-4, 12-17, and 19-43 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

3. The rejection of claims 1-4 and 20-43 under 35 U.S.C. 112, second paragraph, is withdrawn as Applicant has amended the claims to overcome this rejection.

Claim Rejections Withdrawn - 35 USC § 103(a)

4. The rejection of claims 1-4, 23, 29, and 41 under 35 U.S.C. 103(a) as being unpatentable over Morita et al (Jan. 2002, cited on the IDS), Braasch et al. (2001), and Orum et al. (1999, noting this is reference no. 29 of Braasch et al.) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection and in view of claim interpretation, given below.
5. The rejection of claims 12-14 and 19 under 35 U.S.C. 103(a) as being unpatentable over Morita et al (Jan. 2002, cited on the IDS), Braasch et al. (2001), Orum et al. (1999, noting this is reference no. 29 of Braasch et al.), and Weston et al. (U.S. Patent No. 6,391,593 issued 2002, previously cited) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection and in view of claim interpretation, given below.
6. The rejection of claims 15-17 under 35 U.S.C. 103(a) as being unpatentable over Morita et al (Jan. 2002, cited on the IDS), Braasch et al. (2001), Orum et al. (1999, noting this is reference no. 29 of Braasch et al.), and Weston et al. (U.S. Patent No. 6,391,593 issued 2002, previously cited) is withdrawn. The claims are allowed, see below.
7. The rejection of claims 20-22, 24-28, 30-40, and 42-43 under 35 U.S.C. 103(a) as being unpatentable over Morita et al., Braasch et al., and Orum et al. as applied to claims 1-4 above, and further in view of Stanton et al. (US publication No. 20010034023 published 2001 and previously cited) is withdrawn. Applicant's arguments have been

considered but are moot in view of the new ground(s) of rejection and in view of claim interpretation, given below.

Claim Interpretation

8. Claims 1-4 recite primers "comprising" three parts (a), (b), "and" (c). The reasonable interpretation is that these parts are added one to the other which results in a multitude of claimed primers with an ENA of the resultant primer being at the fourth position from the 3' end or some further interior position (and not at the third position from the 3' end). One begins with part (a) oligonucleotide which is all natural nucleotides except for the ENA at the third position from the 3' end then adds at least one nucleotide of part (c) to the 3' end which thus places the ENA at least at the fourth position from the 3' end. One then adds the nucleotides of part (b) which can be inserted in the sequence of (a) and (c) or placed on either end of that sequence. It is further noted that parts (a) and (b) are not limited to natural nucleotides and thus can be modified nucleotides which include ENA and LNA nucleotides. The over arching "comprising" in the preamble also encompasses additional nucleotides other than those recited in parts (a), (b), and (c) to be added to the primer. The claimed primers contain an ENA in the fourth position and positions inward from the 3' end and may further comprise natural and modified nucleotides.

9. Claims 12-14 recite kits comprising a first oligonucleotide wherein the third nucleotide from the 3' end is an ENA unit and the nucleotide at the 3' end is the first nucleotide, the other nucleotides being natural nucleotides. In other words the

nucleotides other than the first and third nucleotide are natural nucleotides. The reasonable interpretation is that the first nucleotide is either a natural nucleotide or non-natural nucleotide which may be an ENA unit. Thus the claims encompass oligonucleotides where the first and the third nucleotides are ENA units.

Data Regarding ENA at the third position

10. Applicant presents data regarding ENA versus LNA substitution at the third position in Remarks filed 12/28/2009 and in the already considered Affidavit filed 02/20/2009. However, as these data regard primers having one and only one ENA substitution at the third position from the 3' end; the data are not specifically relevant to the instant claims. Claims 1-14 encompass primers with at least one ENA at the fourth position from the 3' end and other ENA and LNA substitutions, Claims 15-17 encompass oligonucleotides with ENA units at the first and third positions from the 3' end. Furthermore, as given in the rejections below, the prior art teaches primers with single and multiple ENA substitutions at any position(s) including the fourth position and both the first and third positions and teaches the superior properties of ENA substitutions over LNA substitutions. Thus and as given below, the claimed inventions of claims 1-4 and 12-14 were obvious in view of the prior art

Intention of the Claim Recitations

11. If Applicant intends claims 1-4 to encompass only primers with one ENA at the third position from the 3' end with the other nucleotides being natural nucleotides, then the claims should be amended to recite this. Applicant may wish to consider reciting "consisting of" rather than "comprising" language and may wish to consider eliminating

recitations where parts are added together or which allow insertions, which recitations would change the initial third position of the ENA.

If Applicant intends the claims 12-14 to encompass only primers with one ENA at the third position from the 3' end with the other nucleotides being natural nucleotides, then the claims should be amended to recite this. Applicant is further advised that any claim amendments may require further consideration and/or a new search.

New Rejections

New Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 1-4, 23, 29, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneko et al. (United States Patent Application 20020147332 published October 10, 2002), Morita et al. (Jan. 2002, previously cited), Braasch et al. (2001, previously cited), and Orum et al. (1999 previously cited and noting this is reference no. 29 of Braasch et al.).

Regarding claim 1, 2, 23, and 29, Kaneko et al. teach oligonucleotides used as primers (entire publication, especially claim 84) comprising:

(a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit (see Formula 2 in claim 1) which is the third nucleotide from the 3'-end of the oligonucleotide (see paragraph 0613 and SEQ ID

NO: 3), wherein there may a single ENA unit in the oligonucleotide and the other nucleotides are natural nucleotides (see claims 62, 72, 78, 84, 92, 96, and 102 and paragraphs 0016, 0089, 0182) as especially noted below where:

"[0089] In other certain particularly preferred oligonucleotide analogues, the total number of nucleosides is from 5 to 100, and the entire oligonucleotide analogue comprises (a) one or more of the nucleoside analogues of the formula (2) [ENA unit] and one or more nucleosides selected from the group consisting of (b) a 2'-deoxynucleoside [natural nucleotides]. . . "

(b) a nucleotide complementary to the reference nucleotide of a target gene at the 3'-end position thereof (see claim 78); and

(c) nucleotides complementary to: a nucleotide sequence of the target gene in other positions (see claim 78 for a probe to a gene and necessarily complementary to the gene), a mutant nucleotide (see paragraph 0093), a disease associated gene (see paragraph 0132), or
a salt thereof,

wherein the oligonucleotide has a base length of 5 to 100 bases which encompasses the range of 18 to 25 bases (see paragraph 0089).

It is noted that the intended uses of the oligonucleotides carry no patentable weight.

Regarding claims 1, 2, 23, and 29, Kaneko et al. teach an ENA unit at the first through third positions from the 3' end and teach a single ENA in an oligonucleotide with the other bases being natural nucleotides; but do not specifically teach where the fourth nucleotide from the 3' end is an ENA unit.

Regarding claims 1, 2, 5, 23, and 29, Morita et al. (2002) teach oligonucleotides comprising:

- (a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (entire article, especially the last Figure 1 where X is the ENA unit designated as eT);
- (b) a nucleotide complementary to the reference nucleotide of a target at the 3'-end position thereof (see the Table 1); and having
- (c) nucleotides complementary to a nucleotide sequence of the target in other positions (see the Table 1).

It is noted that elements (b) and (c) are "intended uses" and carry no patentable weight. However, Morita et al. teach certain of these elements as noted above.

Regarding claims 1, 2, 5, 23, and 29, Morita et al. (2001) do not specifically teach an ENA unit at the fourth position from the 3' end; do not specifically teach the "intended use" of nucleotides complementary to a gene which is a target, a target gene; and do not specifically teach a mutant nucleotide. Morita et al. suggest but do not specifically teach for a single oligonucleotide, both a sole ENA at the second position from the 3' end and the "intended use" of the nucleotides being complementary. Morita et al. teach these "intended uses" for two separate oligonucleotides as given respectively in Figure 1 and Table 1.

Regarding claims 1, 2, 5, 23, and 29, Braasch et al. teach an oligonucleotide of 18 to 25 bases (see Table 3) comprising:

- (a) 2'-O,4'-C-methylene nucleotide (LNA) units (see Figure 1) which can be the fourth nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 3 and see Table 1 of Orum et al.); and
- (b) a nucleotide complementary to the reference nucleotide of a target gene of Factor V at the 3'-end position thereof (see Table 3 for various position, especially the first three oligonucleotides and entries 9-12 from the bottom) which can be the mutant nucleotide, the mutation of the Factor V gene (see 3rd paragraph on p. 6), and
- (c) nucleotides complementary to the nucleotide sequence of the target genes of the disease causing Factor V gene (where individuals see 3rd paragraph on p. 6, see Abstract for the general teaching of LNA substituted oligonucleotides which are complementary to genes, and as evidenced in the last sentence on p. 1898 of Orum et al.).

Regarding claims 3-5 and 41, Braasch et al. teach oligonucleotides of 18 to 25 bases (see Table 3) comprising:

- (a) a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the reference/wild type nucleotide of a target gene and teach a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to

the mutant nucleotide of a target gene (see Table 3 especially 9th and as evidenced throughout Orum et al., especially Table 1),

(b) wherein a nucleotide which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and wherein the second nucleotide of each oligonucleotide of claims 3 and 4 is a nucleotide that is not complementary respectively to the nucleotide of a reference/wild type gene and the mutant gene (see Table 1 of Orum et al.).

(c) nucleotides complementary to the nucleotides of the target gene at other positions; and

(d) a nucleotide which is the fourth or fifth nucleotide from the 3'-end of each oligonucleotide is an LNA unit (see Table 1 of Orum et al.).

Regarding claims 1-5, Braasch et al. and Orum et al. teach multiple and various positions and arrangements of LNA units but do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit, and do not specifically teach all of the limitations and intended uses of the claimed oligonucleotide in a single oligonucleotide but with LNA units. Braasch et al. and Orum et al. do teach the limitations and intended uses of the claims but in different oligonucleotides and with LNA units instead of ENA units.

Regarding claims 1-4, Morita et al. teach both 2'-O,4'-C-methylene nucleotide (LNA) units and 2'-O,4'-C-ethylene nucleotides (ENA) units (entire article, especially the Abstract). Morita et al. further teach that substitution of ENA units for LNA units leads to

improved properties of oligonucleotides, including: *{i}* having a high binding affinity for complementary RNA and *{ii}* being more nuclease-resistant than natural DNA and BNA/LNA (see Abstract).

Regarding claims 1-4, Morita et al. teach an oligonucleotide comprising an ENA unit at the second position from the 3' end, but do not specifically teach an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Kaneko et al. teach ENA units (entire publication), teach that they can be placed in any position in a primer, teach that the remaining nucleotides can be natural bases. Furthermore, Kaneko et al. teach that modified nucleotides including ENA units are useful as an antisense or antigene pharmaceutical having excellent stability, a detection agent (probe) for a specific gene, a primer for starting amplification or as intermediates for their production (see paragraph 0009).

Braasch et al. and Orum et al. teach several oligonucleotides comprising LNA units at the fourth position from the 3' of an oligonucleotide. Braasch et al. and Orum et al. do not specifically teach ENA units. Morita et al. teach that oligonucleotides can comprise either LNA units or ENA units. Furthermore Morita et al. teach that substitution of ENA units for LNA units in an oligonucleotide results in improved properties of that nucleotide. Additionally Kaneko et al. teach that an ENA unit may be placed in any position in an oligonucleotide. Because both Braasch et al. and Orum et al. because Morita et al. all teach oligonucleotides comprising LNA units, and Kaneko et al. further teach ENA units can be in any positions in an oligonucleotide; it would have

been obvious to one skilled in the art to substitute an ENA unit as taught by Morita et al. for the LNA unit as taught by Braasch et al. and Orum et al. in order to achieve the predictable result of an oligonucleotide comprising an ENA unit at the fourth or other position(s) from the 3' end.

Furthermore, Braasch et al. and Orum et al. teach that LNA are a valuable tool kit for nucleic acid recognition and chemical genetics (see last sentence). Morita et al. additionally teach the use of ENA units can be further optimized including for improved nuclease resistance (see last paragraph). Kaneko et al. teach that ENA units are useful as an antisense or antigene pharmaceutical having excellent stability, a detection agent (probe) for a specific gene, a primer for starting amplification or as intermediates for their production (see paragraph 0009). Thus, it would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to place an ENA at a fourth or other inward position from the 3' end of oligonucleotides as disclosed by Applicant instead of the second position as used by Morita et al. since these differences in position would not be expected to greatly alter the properties of the oligonucleotides. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the position of the ENA unit could be adjusted to maximize the desired results, as each of Braasch et al. and Orum et al. disclose general and varied positions for LNA units

including the fourth position and Morita et al. and Kaneko et al. also disclose varying positions for ENA units and that substitution of ENA units of LNA units is desirable owing to the improved properties of ENA units in oligonucleotides. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the fourth position for the ENA unit over the second position was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art, especially in regards to the properties of ENA units. As noted, a skilled artisan would expect an ENA unit at the fourth position to have nearly identical properties of ENA units as the second position for oligonucleotides. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

14. Claims 12-14, 19, and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneko et al. (United States Patent Application 20020147332 published October 10, 2002), Morita et al (Jan. 2002, previously cited), Braasch et al. (2001, previously cited), Orum et al. (1999 previously cited, noting this is reference no. 29 of Braasch et al.), and Weston et al. (U.S. Patent No. 6,391,593 issued 2002, previously cited).

Regarding claim 12-14, Kaneko et al. teach oligonucleotides used as primers (entire publication, especially claim 84) and teach kits comprising primers (see paragraph 0112) comprising:

(a) a 2'-0,4'-C-ethylene nucleotide (ENA) unit (see Formula 2 in claim 1) which is the third nucleotide from the 3'-end of the oligonucleotide (see paragraph 0613 and SEQ ID NO: 3 having three ENA units in positions one to three from the 5' end), wherein there may a single ENA unit in the oligonucleotide and the other nucleotides are natural nucleotides (see claims 62, 72, 78, 84, 92, 96, and 102 and paragraphs 0016, 0089, 0182) as especially noted below where:

"[0089] In other certain particularly preferred oligonucleotide analogues, the total number of nucleosides is from 5 to 100, and the entire oligonucleotide analogue comprises (a) one or more of the nucleoside analogues of the formula (2) [ENA unit] and one or more nucleosides selected from the group consisting of (b) a 2'-deoxynucleoside [natural nucleotides]. . . "

(b) a nucleotide complementary to the reference nucleotide of a target gene at the 3'-end position thereof (see claim 78); and

(c) nucleotides complementary to: a nucleotide sequence of the target gene in other positions (see claim 78 for a probe to a gene and necessarily complementary to the gene), a mutant nucleotide (see paragraph 0093), a disease associated gene (see paragraph 0132), or
a salt thereof,

wherein the oligonucleotide has a base length of 5 to 100 bases which encompasses the range of 18 to 25 bases (see paragraph 0089).

It is noted that the intended uses of the oligonucleotides carry no patentable weight.

Regarding claims 12-14, Kaneko et al. teach an ENA unit at the first through third positions from the 3' end and teach a single ENA in an oligonucleotide with the other bases being natural nucleotides; but do not specifically teach where the first and third nucleotide from the 3' end is an ENA unit and the other nucleotides are natural nucleotides. Kaneko et al. teach kits for amplification but not specifically teach kits comprising a DNA polymerase and a PCR buffer.

Regarding claims 12-14, Morita et al. (2002) teach oligonucleotides comprising:

- (a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (entire article, especially the last Figure 1 where X is the ENA unit designated as eT);
- (b) a nucleotide complementary to the reference nucleotide of a target at the 3'-end position thereof (see the Table 1); and having
- (c) nucleotides complementary to a nucleotide sequence of the target in other positions (see the Table 1).

It is noted that elements (b) and (c) are "intended uses" and carry no patentable weight. However, Morita et al. teach certain of these elements as noted above.

Regarding claims 12-14, Morita et al. (2001) do not specifically teach an ENA unit at the third position from the 3' end; do not specifically teach the intended use of nucleotides complementary to a gene which is a target, a target gene; and do not specifically teach a mutant nucleotide. Morita et al. suggest but do not specifically teach for a single oligonucleotide, both a sole ENA at the second position from the 3' end and the "intended use" of the nucleotides being complementary. Morita et al. teach these "intended uses" for two separate oligonucleotides as given respectively in Figure 1 and Table 1.

Regarding claims 12-14, Morita et al. do not specifically teach a kit.

Regarding claims 12, 13, 19, and 52, Braasch et al. teach an oligonucleotide of 18 to 25 bases (see Table 3) comprising:

- (a) 2'-O,4'-C-methylene nucleotide (LNA) units (see Figure 1) which can be the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 3 and see Table 1 of Orum et al.); and
- (b) a nucleotide complementary to the reference nucleotide of a target gene of Factor V at the 3'-end position thereof (see Table 3 for various position, especially the first three oligonucleotides and entries 9-12 from the bottom) which can be the mutant nucleotide, the mutation of the Factor V gene (see 3rd paragraph on p. 6), and
- (c) nucleotides complementary to the nucleotide sequence of the target genes of the disease causing Factor V gene (where individuals see 3rd paragraph on p. 6, see

Abstract for the general teaching of LNA substituted oligonucleotides which are complementary to genes, and as evidenced in the last sentence on p. 1898 of Orum et al.).

(b) a second oligonucleotide which is a reverse primer (see 4th paragraph on p. 1900 of Orum et al.),

(c) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and

(d) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 14, 19, and 53, Braasch et al. teach oligonucleotides of 18 to 25 bases (see Table 3) comprising:

(a) a first oligonucleotide which is a primer/probe wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Table 3 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900), the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 3 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900), wherein the forward primer/probe can be one which is either complementary to the reference/wild type gene or the mutant gene (see last entry in Table 1 and see Orum et al.) and where the gene polymorphism is a single nucleotide polymorphism/single point mutation (see last sentence of the 1st paragraph on p. 1899 of Orum et al.) in the disease causing gene of Factor V gene at the other positions (see 3rd paragraph on p. 1899 of Orum et al. and see title of reference no. 7); and

- (b) a second oligonucleotide which is forward primer 2/probe wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);
- (c) a third oligonucleotide which is reverse primer 1/probe capable of amplifying a sequence of interest together with the forward primer 1/probe (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900),
- (d) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and
- (e) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 15, 16, 19, and 54, Braasch et al. teach an oligonucleotides of 18 to 25 bases (see Table 3) comprising:

(a) a first oligonucleotide which is a forward primer/probe having

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism/single point mutation (see last sentence of the 1st paragraph on p. 1899 of Orum et al.) in the disease causing gene of Factor V gene at the other positions (see 3rd paragraph on p. 1899 of Orum et al. and see title of reference no. 7).;

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(iii) the other nucleotides are complementary respectively to the nucleotides of the target gene and mutant gene (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900); and

(iv) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(b) a second oligonucleotide which is one of the reverse primers/probe capable of amplifying a sequence of interest together with the forward primers (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(c) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and

(d) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 19 and 54, Braasch et al. teach an oligonucleotide of 18 to 25 bases (see Table 3) comprising:

((a) a first oligonucleotide which is a forward primer/probe having

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism/single point mutation (see last sentence of the 1st paragraph on p. 1899 of Orum et al.) in the disease causing gene of Factor V gene at the other positions (see 3rd paragraph on p. 1899 of Orum et al. and see title of reference no. 7).;

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(iii) the other nucleotides are complementary respectively to the nucleotides of the target gene and mutant gene (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900); and

(iv) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(b) a second oligonucleotide having a

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(iii) the other nucleotides are complementary respectively to the nucleotides of the target gene and mutant gene (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900); and

(ii) forward primer 3/probe wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(c) a third oligonucleotide which is any one of the respective reverse primers capable of amplifying a sequence of interest together with the forward primer (see Table 1 and see Orum et al., especially the last paragraph on p. 1899 continued to 1900);

(d) the Taq DNA polymerase (see 4th paragraph on p. 1900 of Orum et al.), and

(e) a PCR buffer (see 2nd sentence on p. 1900 of Orum et al.).

Regarding claims 12-14, Orum et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit and do not specifically teach a kit. Braasch et al. teach a general kit (see last sentence) but do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit.

Regarding claims 12-14, Morita et al. teach both 2'-O,4'-C-methylene nucleotide (LNA) units and 2'-O,4'-C-ethylene nucleotides (ENA) units (entire article, especially the Abstract). Morita et al. further teach that substitution of ENA units for LNA units leads to improved properties of oligonucleotides, including: *{i}* having a high binding affinity for complementary RNA and *{ii}* being more nuclease-resistant than natural DNA and BNA/LNA (see Abstract).

Regarding claims 12-14, Morita et al. teach an oligonucleotide comprising an ENA unit at the second position from the 3' end, but do not specifically teach an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Regarding claims 12-14, Kaneko et al. teach an oligonucleotide with one or more ENA units at any position comprising an ENA unit including the first and third positions from the 3' end, and thus suggest but do not specifically teach an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Braasch et al. and Orum et al. teach several oligonucleotides comprising LNA units at the third position from the 3' of an oligonucleotide. Braasch et al. and Orum et al. do not specifically teach ENA units. Morita et al. teach that oligonucleotides can

comprise either LNA units or ENA units. Kaneko et al. teach that ENA units may in any position in an oligonucleotide. Furthermore Morita et al. teach that substitution of ENA units for LNA units in an oligonucleotide results in improved properties of that nucleotide. Because both Braasch et al. and Orum et al. and because Morita et al. all teach oligonucleotides comprising LNA units, and Kaneko et al. further teach ENA units can be in any positions in an oligonucleotide; it would have been obvious to one skilled in the art to substitute an ENA unit as taught by Morita et al. and Kaneko et al. for the LNA unit as taught by Braasch et al. and Orum et al. in order to achieve the predictable result of an oligonucleotide comprising an ENA unit at the third position from the 3' end.

Furthermore, Braasch et al. and Orum et al. teach that LNA are a valuable tool kit for nucleic acid recognition and chemical genetics (see last sentence). Morita et al. additionally teach the use of ENA units can be further optimized including for improved nuclease resistance (see last paragraph). Thus, it would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to place an ENA at the first and third positions from the 3' end of oligonucleotides as disclosed by Applicant instead of the second position as used by Morita et al. or the first through third positions of Kaneko et al. since these differences in position would not be expected to greatly alter the properties of the oligonucleotides. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would

have recognized that the position of the ENA unit could be adjusted to maximize the desired results, as each of Braasch et al. and Orum et al. disclose general and varied positions for LNA units including the third position and Morita et al. and Kaneko et al. also disclose varying positions for ENA units and that substitution of ENA units of LNA units is desirable owing to the improved properties of ENA units in oligonucleotides. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the first and third positions for the ENA unit over the second position was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art, especially in regards to the properties of ENA units. As noted, a skilled artisan would expect an ENA unit at the first and third position to have nearly identical properties of ENA units in the second position for oligonucleotides or the first through third positions. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

Regarding claims 12-14, Weston et al. teach kits comprising oligonucleotides with LNA units, DNA polymerases, and PCR buffers (see column 7 lines 41-51 and see claims 20 and 21).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the oligonucleotides of Kaneko et al., Morita et al., Braasch et al., and Orum et al. by incorporating them in a kit as suggested by Weston et al. with a reasonable expectation of success. The motivation to do so is provided by Weston et al. who teach the convenience and advantage of kits comprising oligonucleotides, DNA polymerase, and PCR buffers (see column 7 lines 41-51). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

15. Claims 20-22, 24-28, 30-40, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneko et al., Morita et al., Braasch et al., and Orum et al. as applied to claims 1-4 above, and further in view of Stanton et al. (US publication No. 20010034023 published 2001 and previously cited).

Kaneko et al., Morita et al., Braasch et al., and Orum et al. teach as noted above.

Kaneko et al., Morita et al., Braasch et al., and Orum et al. do not teach the limitations of claims 20-22, 24-28, 30-40, and 42-43.

Regarding claims 20-22, 24-28, 30-40, and 42-43 Stanton et al. teach oligonucleotides/primers for detecting drug metabolizing genes (entire publication,

especially paragraph 0143) which are glutathione transferase, N-acetyltransferase (see paragraph 0262), Human cytochrome P4502C9 (see Table 2121 at paragraph 1058)) which are associated with Alzheimer's disease (see paragraph 0023) and teach the target gene which is HLA (see paragraph 0760).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the oligonucleotides of Kaneko et al., Morita et al., Braasch et al., and Orum et al. by making oligonucleotides to detect drug metabolizing genes as suggested by Stanton et al. with a reasonable expectation of success. The motivation to do so is provided by Stanton et al. who teach that such oligonucleotides can be used in methods: ". . . for identifying and utilizing variances in genes relating to efficacy and safety of medical therapy and other aspects of medical therapy" (see Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Allowable Subject Matter

16. Claims 15-17 are allowed.
17. Claim 19 would be allowable if there was no dependency on claims 12-14.
18. The following is a statement of reasons for the indication of allowable subject matter. The claims recite kits comprising a first oligonucleotides with only one ENA unit which is at the third position from the end with the first oligonucleotide having a property not possessed by the prior art (See MPEP § 716.02(a) III. [R-2]). The recited first oligonucleotides have the superior property of reducing non-complementary binding to a

target sequence as given in the original specification, in the Remarks filed 12/28/2009, and in the Affidavit filed 02/20/2009. No prior art was found which teaches or fairly suggests this property. The closest prior art is the combined teachings of Kaneko et al. (2002), Morita et al. (Jan. 2002, Braasch et al. (2001), and Orum et al. (1999) who in combination teach oligonucleotides comprising an ENA unit at any position in an oligonucleotide or primer and teach the remaining nucleotides may be natural bases. However, Kaneko et al., Morita et al., Braasch et al., and Orum et al. each alone or in combination fail to teach or fairly suggest the property disclosed in the instant application.

It is noted that each of claims 15-17 recite at least one oligonucleotide limited to having only one ENA unit which is at third position from the 3' end with the remaining nucleotides being natural nucleotides.

19. As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

Conclusion

20. Claims 15-17 are allowed.

21. Claims 1-4, 12-14, and 19-43 are not free of the prior art.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-

9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
January 27, 2010